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I, KIM MARSHALL , MANAGER EXAMINATION SUPPORT AND SALES, hereby certify that the annexed are true copies of the Provisional specification and drawing(s) as filed on 13 November 1996 in connection with Application No. PO 3593 for a patent by CENTENARY INSTITUTE OF CANCER MEDICINE AND CELL BIOLOGY.

I further certify that the above application is now proceeding in the name of AMRAD OPERATIONS PTY LTD pursuant to the provisions of Section 113 of the Patents Act 1990.

I further certify that the annexed documents are not, as yet, open to public inspection.

PRIORITY DOCUMENT

WITNESS my hand this Eighteenth day of March 1998

KIM MARSHALL
MANAGER EXAMINATION SUPPORT AND SALES

Centenary Institute of Cancer Medicine and Cell Biology

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"A Method of Treatment and Pharmaceutical Compositions Useful for Same"

The invention is described in the following statement:

A METHOD OF TREATMENT AND PHARMACEUTICAL COMPOSITIONS USEFUL FOR SAME

The present invention relates generally to a method of ameliorating the effects of autoimmne conditions and pharmaceutical compositions useful for same. More particularly, the present invention provides a method for preventing, delaying onset of or otherwise ameliorating the effects of insulin-dependent diabetes mellitus (IDDM) by administering a cell wall subunit or a chemical or functional equivalent thereof from *Mycobacterium* or a related organism or other suitable biological source. The present invention is further directed to a pharmaceutical composition useful in preventing, delaying onset of, curing, curing in association with islet replacement or otherwise ameliorating the effects of IDDM comprising a cell wall subunit or a chemical or functional equivalent thereof from *Mycobacterium* or a related organism or other suitable biological source.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Bibliographic details of the publications numerically referred to in this specification are collected at the end of the description.

Insulin-dependent diabetes mellitis (IDDM) is a debilitating, chronic, cell-mediated autoimmune disease characterised by lymphocytic infiltration of the pancreatic islets and T lymphocyte-mediated destruction of insulin-producing β cells (1, 2).

Non-obese diabetic (NOD) mice are a valuable model in studying IDDM as they spontaneously develop the disease which has many immunological and pathological similarities to human IDDM (3, 4).

It has been previously shown that administration of Freund's complete adjuvant (FCA) or *Mycobacterium bovis* (Bacillus Calmette-Guerin (BCG3) [3]) prevents development of diabetes in NOD mice (5, 6). However, Baxter *et al* (7) showed the administration of BCG although preventing diabetes in NOD mice, precipitated a syndrome similar to systemic lupus erythematosus (SLE), precluding its use in humans.

In accordance with the present invention, it has been shown that a subunit complex from the cell wall of *Mycobacterium* prevents diabetes in NOD mice without risk of precipitating SLE.

Accordingly, one aspect of the present invention contemplates a method of preventing, delaying onset of, curing or otherwise ameliorating the effects of an autoimmune disease in a mammal said method comprising administering to said mammal an autoimmune-preventing effective amount of one or more components of the cell wall of *Mycobacterium* or a related organism or analogous components from another biological source.

Autoimmune conditions contemplated by the present invention include but are not limited to IDDM, thyroiditis, atrophic gastritis (type A), pernicious anaemia, Addison's disease, pemphigus vulgaris, pemphigoid, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, discoid lupus erythematosus, haemolytic anaemia, sympathetic ophthalmia, uveitis, idiopathic thrombocytopenia, idiopathic leucopenia, primary biliary cirrhosis, autoimmune chronic active hepatitis, ulcerative colitis, Sjogren's syndrome, dermatomyositis, scleroderma and mixed connective tissue disease.

The present invention is hereinafter described in relation to IDDM but this is done with the understanding that the invention extends to autoimmune diseases such as contemplated above.

Accordingly, the present invention particularly contemplates a method of preventing, delaying onset of, curing, curing in association with islet replacement or otherwise ameliorating the effects of IDDM in a mammal said method comprising administering to said mammal an IDDM-preventing effective amount of one or more components of the cell wall of *Mycobacterium* or a related organism or analogous components from another biological source.

The components of the *Mycobacterium* cell wall or other suitable source contemplated for use in preventing IDDM in mammals include the mycolyl-arabinogalactan-peptidoglycan (mAPG) complex with or without other associated cell wall components and submolecular components or mAPG, mycolate, arabinogalactan and/or peptidoglycan or derivatives thereof. The structure of a *Mycobacterium* cell wall is summarized in Figure 1. The mAPG or its components may be in native or chemically synthetic form. mAPG is a complex of covalently attached macromolecules. Mycolic acids are covalently attached to arabinogalactan which is in turn covalently attached to peptidoglycan. Reference herein to "mAPG" includes the mAPG complex isolated from *Mycobacterium* or related organism or other suitable biological source or to a chemically or functionally equivalent complex as well as submolecular components including mycolic acids, peptidoglycan or arabinogalactan or chemical or functional equivalents thereof. The submolecular components may be in isolated form or in partial complex forms such as comprising mycolic acid and arabinogalactan, arabinoglactan and peptidoglycan or mycolic acids and peptidoglycan or chemical or functional equivalents thereof. A particular complex may also comprise, for example, mycolic acids covalently linking to arabinogalactan and this may in turn be covalently linked to a portion or derivative of peptidoglycan.

A convenient source of mAPG or its components is *Mycobacterium bovis* or BCG. The present invention, however, extends to mAPG or its components from any species of *Mycobacterium* or from physiologically, genetically, biochemically or structurally related microorganisms. Examples of similar organisms include *Actinomycetes*, *Nocardia* and *Corynebacterium.* A similar molecule or natural complex or components thereof may also be isolatable for other biological sources such as plants and coral. The mAPG complex or its components may be isolated from mycobacterial cell envelopes prepared, for example, by the method of Azuma *et al* (8)

According to this aspect of the present invention, there is provided a method for isolating components of mAPG for use in a therapeutic composition for preventing, delaying the onset of or otherwise ameliorating the effects of diabetes in a mammal, said method comprising preparing cell envelopes from a species of *Mycobacterium* or related organism or other suitable biological source, subjecting said cell envelopes to glycolipid removing means to remove soluble

glycolipids, treating the product so obtained to break the mycolic acid linkage and isolating said mycolic acid, treating the remaining complex to cleave linkage at rhamnose residue connecting arabinogalactan to the peptidoglycan backbone and separating and isolating arabinogalactan and peptidoglycan.

The soluble glycolipids are conveniently removed by repeated centrifugation in the presence of sodium dodecyl sulphite (SDS). The resulting insolvent envelope mAPG complex is then subjected to fractionation.

The mycolic acid linkage is preferably cleaved by saponification, base-catalysed methanolysis or ammonolysis. The remaining complex of arabinogalactan and peptidoglycan is preferably then subjected to a Smith degradation comprising periodate followed by borohydride reduction and mild acid treatment.

The mAGP complex or its component parts or derivatives thereof may be in any convenient form such as vacuum dried, powder, liquid or slurry.

The present invention further contemplates a composition of matter comprising mAPG or a derivative thereof or a component thereof or its derivative. These components are referred to herein as "active ingredients".

Preferably, the composition is a pharmaceutical composition for use in preventing, delaying onset of, curing, curing in association with islet replacement or otherwise ameliorating the effects of IDDM in mammals. The pharmaceutical composition may additionally comprise one or more pharmaceutically acceptable carriers and/or diluents.

According to this and other aspects of the present invention, preferred mammals include humans, primates, livestock animals (eg. cows, horses, sheep, pigs, donkeys), laboratory test animals (eg. mice, rabbits, guinea pigs, hamsters), companion animals (eg. dogs, cats) and captive wild animals (eg. kangaroos, foxes, deer).

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion or may be in the form of a cream or other form suitable for topical application. The present invention also contemplates administration *via* topically applied compositions where molecules are used to permit entry *via* the skin. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol and the like), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as licithin, by the maintenance of the required particle size in the case of dispersion and by the use of superfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thirmerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with

food material (including solid or liquid products). For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 μg and about 2000 mg of active compound. Other ranges contemplated herein include from about 1μg to about 1000 mg, from about 10 μg to about 100 mg and from about 100 μg to about 50 mg.

The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter: a binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such a sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations.

The present invention also extends to forms suitable for topical application such as creams, lotions and gels.

Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion

media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 0.1 µg to about 2000 mg. Expressed in proportions, the active compound is generally present in from about 0.5 µg to about 2000 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

The active ingredients of the present invention may be administered alone or in combination with other therapeutic molecules such as molecules which reduce effects of the autoimmune pathology associated with IDDM. A single dose may be administered or multiple doses may be required with intervals of from minutes to hours, daily to weekly or monthly to yearly.

Reference herein to "preventing" IDDM includes total prevention of IDDM or substantial

prevention for a limited time (eg. from about 1 to about 10 years) or delaying onset of IDDM or reducing the severity or otherwise ameliorating the effects of IDDM.

The present invention is further described by the following non-limiting figures and Examples.

In the Figures:

Figure 1 is a diagrammatic representation of a mycobacterial cell wall showing its various components.

Figure 2 is graphical representation showing percentage incidence of diabetes overtime (days) following administration of:
(a) killed BCG at $2x10^7$ CFU (2 mg; [□]), 1 x 10^7 CFU (1mg; [○]) and $2x10^6$ CFU (0.2 mg; [+]);
(b) phosphate buffered saline (PBS) control.

Figure 3 is a graphical representation showing percentage incidence of diabetes over time (days) following administration of:
(a) GEBU (an adjuvant comprising N-acetylglucosaminyl-N-acetylmuramyl-L-alanyl-D-isoglutamine) at 10 μg (□), 5.0 μg [○] and 2.5 μg [+];
(b) mannose-capped lipoarabinomannan (manLAM) at 50 μg [□], 25 μg [○] and 13 μg[+]; and
(c) mAPG (mycolylarabinogalactan peptidoglycan) at 50 μg [□], 250 μg [○] and 125 μg [+].

EXAMPLE 1

Components of mycobacterial cell wall

The components of the mycobacterial cell wall are shown in Figure 1.

EXAMPLE 2

Mice

Female NOD/Lt//Arc mice were obtained from the Animal Resources Centre (Canning Vale, WA, Australia) and maintained in clean conditions in the Centenary Institute Animal House. Sentinel mice were tested by serology at four-monthly intervals for the following pathogens: mouse hepatitis virus, rotavirus, ectomclia, mouse cytomegalovirus, polyoma virus, murine adenovirus, lymphocytic choriomeningitis virus, mouse pneumonia virus, retrovirus, Sendai virus, Theiler's murine encephalitis virus, *Bacillus piliformis, Mycoplasma pulmonis, Bordetella bronchiseptica, Corynebacterium kutscheri, Klebsiella* species, *Pasturella multocide, Pasturella pneumotropica, Pseudomonas aeruginosa, Straphylococcus aureus, Streptococcus pneumoniae, Citrobacter freundii* and salmonella species. No mice tested positive for any of these pathogens. Mice were housed at 21C and 40% humidity and were fed Barastock mouse chow (Melbourne, VIC, Australia) and acidified water *ad libitum.*

Under these conditions, about 75% of female NOD mice spontaneously developed IDDM by 35 weeks of age. The disease process involved a progressive preclinical phase of islet destruction which commenced at 4-6 weeks of age, and concluded with the onset of clinical diabetes between 14 and 35 weeks of age. Within a population, disease onset occurred in a sigmoidal fashion with the peak incidence of IDDM at 22 weeks of age, and a plateau at 35 weeks after which few previously unaffected mice ever progressed to diabetes (9).

NOD mice intravenously injected with a single dose of 1-4mg of heat-killed BCG did not become diabetic, but developed a lupus-like disease characterised by haemolytic anaemia (indicated by a lowered haematocrit and positive Coombs' test), increased titres of anti-nuclear antibodies (demonstrated by immunofluorescence of HEp-2 cells) and glomerulonephitis (demonstrated by

immunofluorescence of C3c bound to the renal glomeruli) (7).

EXAMPLE 3

BCG therapy

Evans (Langhurst, UK) or CSL (Parkville, Australia) live freeze dried and attenuated *Mycobacterium bovis* (bacillus Calmette-Gucrin; BCG) vaccine was dissolved in isotomic saline and heat inactivated at 65 C for 45 minutes.

EXAMPLE 4

Mycobacterial subfractions

Mannose-capped lipoarabinomannan (ManLAM) and mycolyl-abarbinogalactan-peptidoglycan complex (mAPG) may be prepared as previously described (8). N-aceytlglucoaminyl-N-acetylmuramyl-L-alanyl-D-isogutamine (GERBU) was purchased from a commercial source (GERBU Biotechnik, Gaibery, Germany). Applicant acknowledge with appreciation receiving samples of ManLAM and mAPG from the Tuberculosis Repository by Drs P. J. Brennan and J. T. Belisle through NIAD, NIH [Contract No. NO1-AU1-25147].

EXAMPLE 5

Random blood glucose estimations

Each mouse was bled by retro orbital venepuncture of 100-150 μl and the serum glucose concentration measured by the glucose oxidase technique on a Glucostix reagent strip (Ames, Basingstoke, UK). A mouse was considered to be diabetic if it was found to have a random blood glucose level > 12mMol/l.

EXAMPLE 6

Haematocrit measurement

Seventy-five microlitres of blood were drawn up into a heparinized capillary tube (Hawksley,

Sussex, UK) and centrifuged at 1000g for 15 minutes. The height of the column of packed red cells was divided by the total height of the column of blood and expressed as a percentage.

EXAMPLE 7

Direct Coombs test

Mice were bled and the plasma removed. Ten microlitres of packed cells were resuspended in 5ml PBS with 0.3% w/v bovine serum albumin, washed and resuspended in 1ml of the same solution. Triplicates of 100 μl aliquots were placed in 96 well round bottom plates (Nunc, Denmark) with 3 serial ½ dilutions. The plates were vortexed and incubated at 37 C for 1hr. Wells were then assessed for false positive results. Ten microlitres of 10 μg/ml polycloncal goat anti-mouse IgG (Sigma Chemical Company, MO, USA) added. Plates were then vortexed gently and incubated at 37C for a further two hours. Wells in which the cells collected in a button were recorded as negative, while those in which the cells remained spread of the surface over the well were recorded as positive.

EXAMPLE 8

Assessment of antinuclear antibodies

Sera was assessed for binding to HEp-2 slides (Quantafluor, Chaska, MN, USA). Slides were incubated in phosphate buffered saline (PBS) for 10 minutes. Sera diluted in PBS (starting concentration 1:100) were incubated on the slides at room temperature (RT) for 30 minutes in a moist chamber. Slides were then washed 3 times for 5 minutes in PBS and incubated for 30 minutes at RT with 1:50 FITC conjugated rat anti-mouse Ig (Serotec, Oxford, UK). Slides were again washed 3 times for 5 minutes with PBS, mounted and examined on an Axiophot fluorescence microscope (Zeiss, DDR). Sera from MRL/*lpr-lpr* and BALB/c mice were used as controls.

EXAMPLE 9

Detection of glomerular immune complex deposits

Kidneys were embedded in Tissue-Tek OCT Compound (Miles, Elkhart, IN) and frozen for histological analysis. Sections of 6 μm were cut on a Microm cryostat (Waldorf, Germany) and mounted on microscope slides, air dried, acetone fixed for 10 minutes and stored at -80C in an air-tight bag containing silica desiccant. When slides were stained, they were thawed to room temperature, fixed in acetone for a further five minutes and blocked with 4% v/v foetal calf serum (FCS; CSL, Melbourne, VIC, Australia). Sections were stained with Goat anti-mouse C3c polyclonal IgG (Nordic Immunological Laboratories, Tilburg, Holland) at a 1:10 dilution in PBS for 45 minutes. Slides were then washed three times in PBS, and coverslipped with polyvinyl alcohol mounting media (Sanofi Diagnostics Pasteur Inc., Chaska, MN) and examined on a Leica fluorescence microscope (Leica Mikoskopie, Postfach, Germany).

EXAMPLE 10

Effects of heat killed BCG on incidence of diabetes

Varying concentrations of heat killed *Mycobacterium bovis* (BCG) were administered to NOD mice at $2x10^7$ CFU (2 mg), $1x10^7$ CFU (1 mg) at $2x10^6$ CFU (0.2mg) relative to a control of phosphate buffered saline (PBS). No diabetes was detected in mice given 1 mg or 2 mg of BCG.

EXAMPLE 11

Effects of mycobacterial cell wall components on incidence of diabetes

In order to attempt to separate the activity of BCG which prevented IDDM from that which precipitated lupus, the mycobacterial subfractions GERBU, mAPG and ManLAM were tested for these activities. GERBU (10, 5.0 and 2.5 μg), ManLAM (50, 25 and 13μg), and mAPG (500, 250 and 125μg) were each suspended in saline and injected intravenously into eight week old female NOD mice. These doses of mAPG and ManLAM were based on estimates of the equivalent quantities in 1mg of BCG, while the does of GERBU was based on that used for immunoadjuvant activity; 10μg being the maximum dose tolerated by mice. Groups of 5 mice

were tested and the incidence of diabetes compared to 25 saline treated and 12 BCG treated control mice. The results are shown in Figure 3.

While 21/35 (60%) PBS treated mice, 11/15 (73%) of GERBU treated mice and 8/15 (53%) of ManLAM treated mice developed diabetes, no mice receiving mAPG did so. Haematocrits and Coombs' tested indicated that no mice receiving mAPG developed haemolytic anaemia whereas 8/12 (67%) of BCG treated control mice had a haematocrit below 45% and 6/12 mice were Coombs' test positive. Similarly there was no increase in the expression of antinuclear antibodies in the mAPG treated mice.

EXAMPLE 12

Purification of components of mAPG

Mycobacterium cell envelopes maybe prepared by the method of Azuma *et al* (8) and the soluble glycolipids removed by repeated centrifugation in the presence of SDS. The insoluble envelope component, the peptidoglycan conjugated with mycolic acid-substituted arabinogalactan, is fractionated into its constituent domains by the following procedure.

1. the mycolic acid linkage is cleaved by saponification, base-catalysed methanolysis or ammonolysis and separated from the insoluble residue.

2. the residue is submitted to Smith degradation (periodate, followed by borohydride reduction and mild acid treatment) to cleave the linkage at the rhamnose residue connecting the galactan to the peptidoglycan backbone.

Due to the nature of the furanosyl linkages in the galactan and arabinan domains, these residues are not affected by this treatment. The soluble arabinogalactan separated from the peptidoglycan by centrifugation.

EXAMPLE 13

Testing components of mAPG

The previous example shows the effectiveness of mAPG in preventing development of diabetes relative to other components of the mycobacterial cell wall. The individual constituents of mAPG are purified according to Example 12 and tested at varying concentrations in NOD mice. The incidence of diabetes is then determined over time.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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DATED this 13th day of November 1996

~~CENTENARY INSTITUTE OF~~ AMRAD Operations Pty Ltd

~~CANCER MEDICINE AND CELL BIOLOGY~~

By DAVIES COLLISON CAVE

Patent Attorneys for the Applicants

FIGURE 1

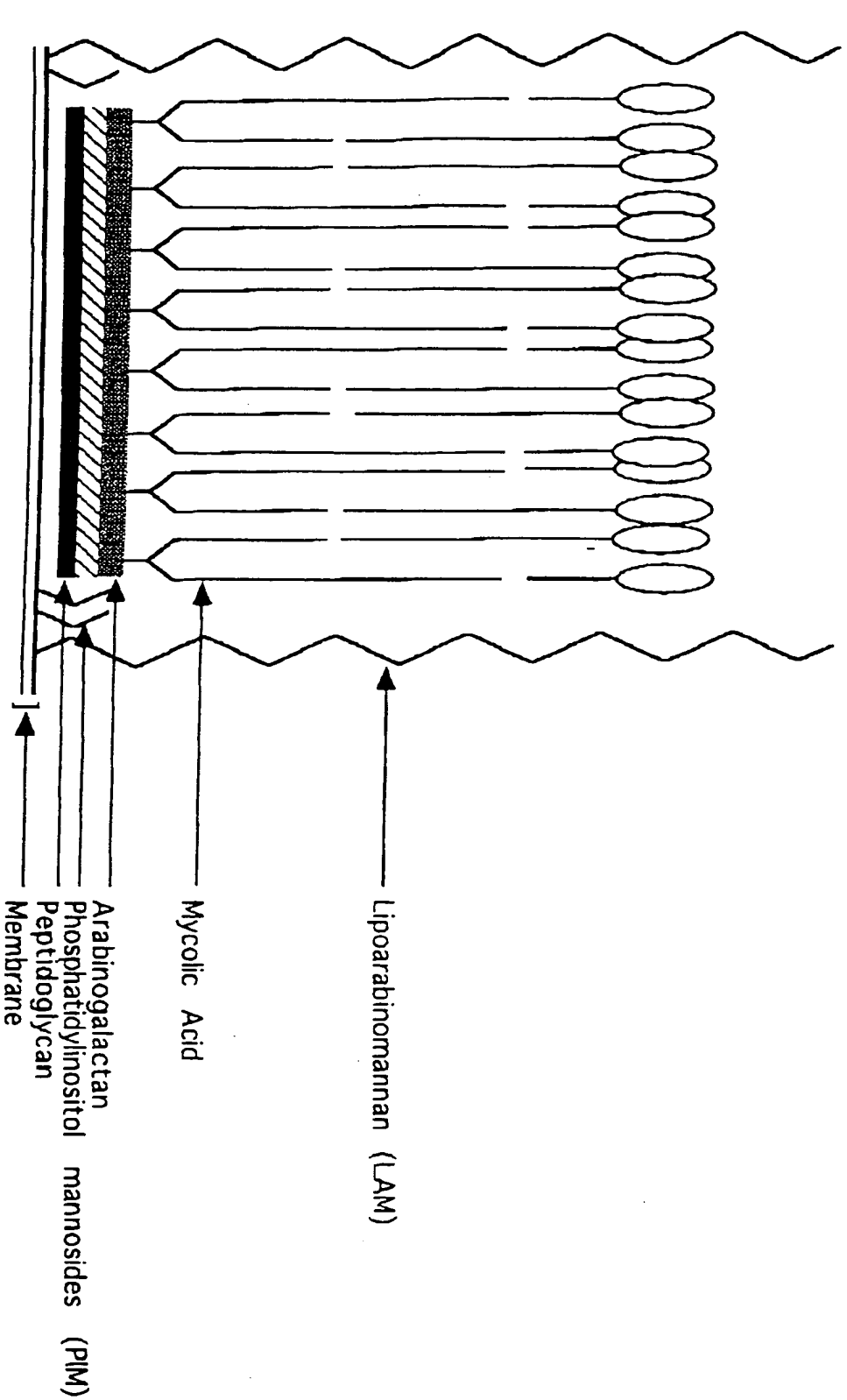
Mycobacterial Cell Wall
Lipoarabinomannan (LAM)
Mycolic Acid
Arabinogalactan
Phosphatidylinositol mannosides (PIM)
Peptidoglycan
Membrane

FIGURE 2(A)

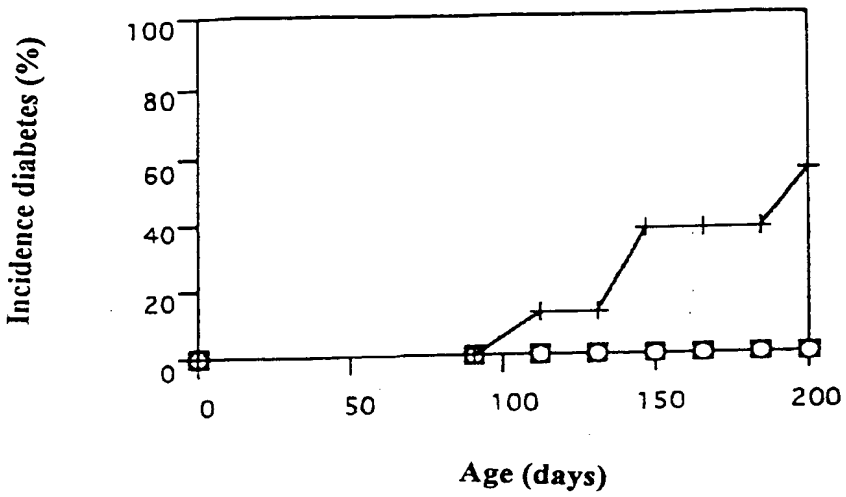

FIGURE 2(B)

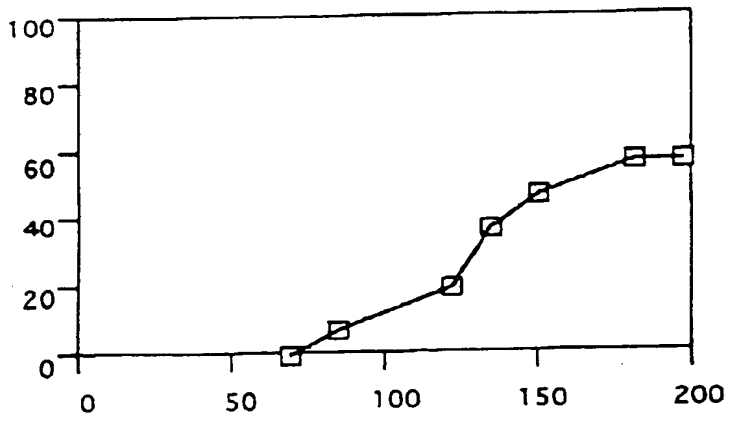

FIGURE 3(A)

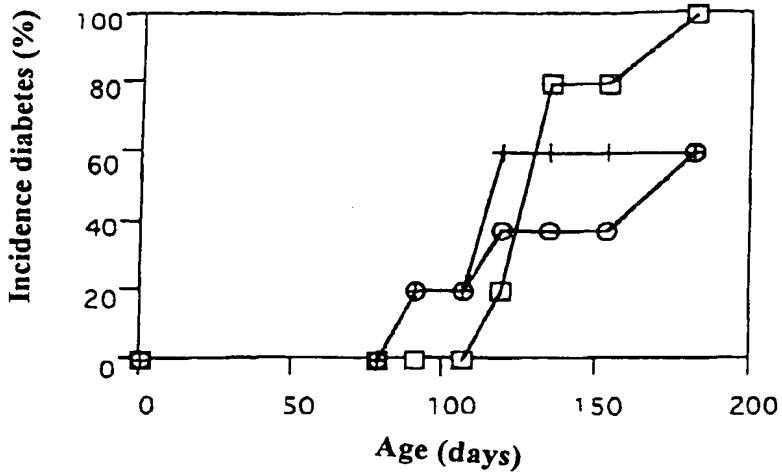

FIGURE 3(B)

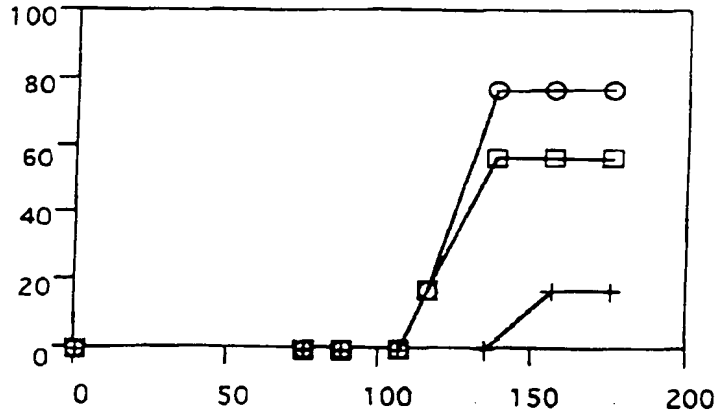

FIGURE 3(C)